# LRRK2 mutations cause mitochondrial DNA damage in iPSC-derived neural cells from Parkinson's disease patients: reversal by gene correction.

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**Public Summary:**
Parkinson's disease associated mutations in leucine rich repeat kinase 2 (LRRK2) impair mitochondrial function and increase the vulnerability of induced pluripotent stem cell (iPSC)-derived neural cells from patients to oxidative stress. Since mitochondrial DNA (mtDNA) damage can compromise mitochondrial function, we examined whether LRRK2 mutations can induce damage to the mitochondrial genome. We found greater levels of mtDNA damage in iPSC-derived neural cells from patients carrying homozygous or heterozygous LRRK2 G2019S mutations, or at-risk individuals carrying the heterozygous LRRK2 R1441C mutation, than in cells from unrelated healthy subjects who do not carry LRRK2 mutations. After zinc finger nuclease-mediated repair of the LRRK2 G2019S mutation in iPSCs, mtDNA damage was no longer detected in differentiated neuroprogenitor and neural cells. Our results unambiguously link LRRK2 mutations to mtDNA damage and validate a new cellular phenotype that can be used for examining pathogenic mechanisms and screening therapeutic strategies.

**Scientific Abstract:**
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